Rejections under 35 U.S.C. § 101 and § 112, first paragraph

Claims 1-11, which are directed to methods for identifying a nematode having enhanced susceptibility to a pathogen, stand rejected under 35 U.S.C. § § 101 and 112, first paragraph. The Examiner asserts that the claimed invention is not supported by a substantial or specific asserted utility or by a well established utility that would enable one skilled in the art to use the invention.

The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) has articulated the standard to be applied by the PTO in any challenge to an assertion of utility. In this case, the Court stated (at page 1566):

> the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. [citation omitted]. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.

As is discussed below, the Office has failed to carry this burden.

In support of this rejection, relying on *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. 689 (1966), the Examiner states:

> The asserted utility of using the nematode for identifying new genes or factors that allow a host to combat infection is an invitation for further research by the skilled artisan. In Brenner, the Court held that materials to be used as an object of research or methods of using those materials as an object for research have raised issues as to whether those materials possess a real world context of substantial utility.

In doing so, the Office improperly applies the holding of *Brenner* by equating the present

invention to that in *Brenner*. Applicants believe that Brenner is inapposite to the facts of the present case.

The invention in *Brenner* was a chemical process that created a homolog of a previously known steroid, where the steroid possessed tumor-inhibiting activity. The homolog in *Brenner* was not shown to have similar tumor-inhibiting characteristics. In fact, no properties of the homolog were provided except for the structural similarity to the previously known steroid. The court affirmed the Board of Appeals decision which stated that the statutory requirement of usefulness of a product cannot be presumed merely because it happens to be closely related to another compound which is shown to be useful. *Brenner*, 148 U.S.P.Q. at 690.

Applicants instead submit that the facts in the present case are more closely aligned with those presented in *In re Folkers*, 334 F.2d 970, 145 U.S.P.Q. 390 (C.C.P.A 1965), a case that may be contrasted with *Brenner*. In *In re Folkers*, the applicants discovered a new hydroquinone and confirmed that, like other hydroquinones, it underwent electron-transfer reactions. The *Folkers* court held that the physicochemical property of electron transfer was sufficient to establish utility under § 101. In reversing the Board's finding of lack of utility, the court stated:

> that [the] usefulness of a chemical compound is invariably a manifestation of a given property of that compound. We think some uses can be immediately inferred from a recital of certain properties. The question here is not whether the property of electron transfer is a use, but whether knowledge of that property necessarily and implicitly renders it readily apparent to one of ordinary skill that the present compounds are useful. (*In re Folkers*, 145 U.S.P.Q. at 394; emphasis added).

The recitation of the physicochemical property of electron transfer distinguished the hydroquinone of *Folkers* from the steroid analog of *Brenner*, which possessed no recited feature other than its chemical structure.

Identifying nematodes with enhanced susceptibility to a pathogen is analogous to the hydroquinone in *In re Folkers*, not to the steroid analog of *Brenner*. Applicants, in addition to identifying the esp enhanced susceptibility genes, demonstrated important properties – that Applicants' screening assays identify genes that protect a host from pathogen infection and therefore are useful identifying host factors that protect an organism from pathogenic disease – a situation analogous to the electron transfer reaction properties of the compound in *Folkers*. Thus, the present invention is therefore distinguished from *Brenner* because Applicants are not relying on any assumed function-by-analogy.

The present case is, instead, analogous to *In re Folkers* where identification of an inherent (biological) property necessarily and implicitly rendered its utility apparent to one of ordinary skill in the art. Here, the identification of host genes that protect against pathogens renders them useful, for example, as drug targets for diseases linked to pathogen infection. Applicants' claimed invention therefore finds substantial utility in a real world context. Indeed, as is disclosed in Applicants' specification, the claimed methods provide "a simple means for identifying host factors and genes that enable a host to combat pathogen infection and compounds capable of . . . . enhancing a host's

resistance capabilities to such pathogens (see, page 22, lines 14-19)." Accordingly, the Examiner's reliance on *Brenner* is misplaced, and the rejection which is based on this case should be reversed.

Applicants further point out that the Revised Interim Utility Guidelines Training Materials outline the criteria to determine the utility of an invention. The utility of an invention must be specific and substantial or well-established. In defining the metes and bounds of a specific utility, the Revised Interim Utility Guidelines Training Materials require that:

> a utility [be] specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention ... A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. (paragraph bridging pages 5 and 6; emphasis added)

By implication, therefore, the specific utility of a particular component such as a gene or protein may be established by the disclosure of a specific disease or condition with which it is associated. Applicants disclose that the methods of the invention are useful for the identification of nucleic acids and proteins associated with host resistance genes to pathogen infection. Pathogen infections, which include bacterial infections by *Pseudomonas aeruginosa* or *Enterococcus faecalis*, constitute specific pathogenic diseases. Applicants disclose that the identified nucleic acids and proteins enable a host to combat pathogen infection or enhance a host's resistance to a pathogen infection (page 6, lines 3-8). Accordingly, on this basis too the utility rejection should be withdrawn.

In addition, Applicants further point out that a substantial utility is established by a "real world" context of use, such as the identification of a material which has a correlation to, or impacts the onset or progression of a particular disease or condition. Specifically, the Revised Interim Utility Guidelines state:

> Both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. (page 6; emphasis added)

Thus, an assay method for identifying candidate compounds which may be used for treating a specific disease itself has substantial utility. Applicants disclose that a nematode having enhanced susceptibility to a pathogen may be used to identify therapeutic compounds for the treatment of a pathogenic infection. Because such nematodes constitute an *in vivo* assay system, they allow for the simultaneous evaluation of host toxicity as well as anti-pathogenic potency, and provide for the identification of compounds that stimulate and strengthen a host's response to pathogenic attack. Accordingly, Applicants screening methods themselves must have a specific and substantial utility.

Alternatively, Applicants point out that the utility requirement of 35 U.S.C. § 101 can be satisfied by identifying a well established utility which is defined in the Revised Interim Utility Guidelines Training Materials as (page 7):

> A specific, substantial, and credible utility which is well known, immediately

apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

Of course, in evaluating the utility of the invention, the credibility of the disclosure must be assessed. Credibility must be viewed from the perspective of a person of ordinary skill in the art and should be based on the totality of the evidence (specification and prior art) and reasoning provided.

Applicants have provided overwhelming evidence showing that mutant nematodes are accepted as model systems for a variety of human diseases, including cancer, diabetes, obesity, and mucolipidosis (see Appendix A, Reply to Office Action filed February 20, 2003). The utility of the nematode as a model system is even accepted by the Nobel Assembly at the Karolinska Institutet, which recognized that a correlation exists between disease pathogenesis in humans and *C. elegans* (see Reply to Office Action filed February 20, 2003). Given this correlation, it is reasonable to expect that the claimed nematodes would also be useful as a model system and that *C. elegans* genes that regulate the nematode's response to pathogen infection have mammalian counterparts. Moreover, as detailed below, Applicants demonstrated that several *C. elegans* enhanced susceptibility genes are mammalian counterparts that function in immunity. In contrast, the Examiner has failed to provide evidence showing why nematodes having mutations in such genes would not be useful.

Moreover, Applicants disclose that *C. elegans* enhanced susceptibility genes, *esp-8* and *esp-2*, encode proteins that correspond to mammalian p38 MAP kinase pathway

genes (page 13). In addition, Applicants disclose that a *C. elegans* homolog of p38, *pmk-1*, functions in *C. elegans* response to pathogens. In mammals, the MAP kinase signaling pathway functions in generating an immune response to combat bacterial infection (e.g., response to bacterial lipopolysacharide and production of cytokines) (Garrington, page 211, second paragraph), just as it does in *C. elegans*. In fact, the *C. elegans* and mammalian pathways are so closely related that the *C. elegans* protein *sek-1* is able to phosphorylate mammalian p38 *in vitro*, just as its mammalian counterpart, MKK3/MKK6, does *in vivo* (page 14, lines 12-15).

In sum, Applicants' claimed methods provide a substantial utility and real world context of use for materials used to treat or diagnose diseases such as pathogenic infection. Indeed, as noted above, based on Applicants' discoveries, Applicants have reasonably asserted that their screening methods find use in the development of drugs or drug screens for pathogenic diseases known to be associated with genes identified to confer enhanced susceptibility to a pathogen. The Examiner has failed to carry the burden, as articulated in *Brana* (see above), to challenge Applicants' assertion of utility. No evidence has been presented explaining why pathogenic disease association is contrary to scientific reasoning. Accordingly, the related rejections under 35 U.S.C. § 101 and § 112, first paragraph should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested.

Enclosed is a petition to extend the period for replying for three months, to and including November 18, 2004. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 18 November 2004

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